# Synopses for the Ph.D. Work

# Investigation of some selective strategies for the synthesis and functionalization of heterocycles

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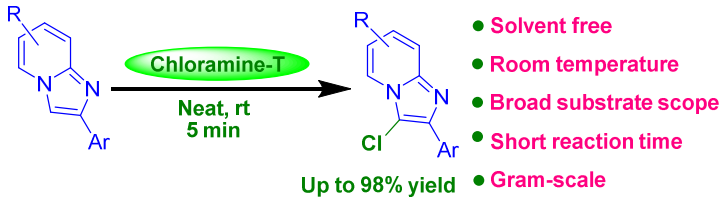
# Investigation of some selective strategies for the synthesis and functionalization of heterocycles

Heterocyclic compounds play significant roles in the biology and pharmaceuticals. The modifications of the core structures provide a great extension to the structural diversity. Because of this, the synthetic procedures of various heterocycles have gained a special attention within combinatorial chemistry, which has experienced to become a primary tool in many aspects of chemistry in general and in drug discovery process in particular. The main objective of the present work is focused on the synthesis and functionalization of furans and imidazopyridine.

## 1. An Environmentally Friendly Protocol for the Chlorination of Imidazoheterocycles by Chloramine-T

### Introduction

An environmentally friendly method for the chlorination of imidazoheterocycles has been developed using chloramine-T, a novel chlorinating reagent. A bunch of C-3 chloro-substituted imidazo[1,2-*a*]pyridines with variety of functionalities have been synthesized in good yields under neat condition at room temperature within very short time. This chlorination process is also applicable to imidazo[2,1-*b*]thiazole scaffolds. The present methodology is relevant to gram-scale synthesis. The major advantages of this system such as wide applicability, easily available reactants, open air, metal and solvent-free reaction conditions, no need of work-up, and simple purification technique represent a green synthetic protocol.




**Scheme 1**

The imidazopyridine, a nitrogen containing important heterocycle moiety, has wide range of biological activities and is found in several marketed drugs. This scaffold is

also successfully employed in the field of material science. As a consequence, different processes have been reported for the synthesis and functionalization of imidazopyridine derivatives. Here in, we report a operationally simple, low-cost, room temperature chlorination reaction using chloramine-T in neat condition within very short time. Chloramine-T is found to be an exceptionally proficient chlorinating agent for the synthesis of 3-chloro-imidazo[1,2-*a*]pyridines under solvent-free conditions and there is no need of column-chromatography for the purification in most of the cases. No over chlorination is found, and a variety of functional groups is tolerated. This chlorination technique is carried out under open air. In short, we have revealed a highly efficient chlorinating reagent, active to imidazoheterocycles in neat condition (Scheme 1).

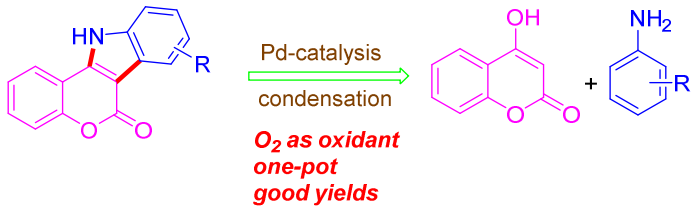
**Conclusion**

In conclusion, we have successfully developed an environmentally benign, efficient and regioselective methodology for the chlorination of imidazo[1,2-*a*]pyridines at room temperature. The proposed method accepts broad substrate scope applicability and allows a wide range of functionality. This technique is also capable to chlorinate the benzo[*d*]imidazo[2,1-*b*]thiazoles. General applicability, easily accessible reagents, operational simplicity, clean reaction, easy purification technique, open air, metal and solvent-free as well as environmentally friendly reaction conditions and high yields are the notable advantages of the present protocol. These features make this convenient practice to be a green synthetic strategy. We belief that this 'green' path will gain much more attention in organic synthesis, academic and industrial field as a powerful and economical route for the chlorination of imidazoheterocycles.

## 2. Palladium-Catalyzed Synthesis of Indole Fused Coumarins *via* Cross-Dehydrogenative Coupling (CDC)

**Introduction**

The present method describes a palladium-catalyzed cross-dehydrogenative coupling reaction for the synthesis of indole fused coumarin derivatives. The one-pot method is operationally simple and molecular oxygen is used as sole oxidant. The target compounds are obtained in good yields from commercially available precursors.




**Scheme 2**

Coumarins are important class of heterocyclic compounds and are interesting to organic and medicinal chemists due to their valuable pharmacological activities, such as, antimicrobials, anti-oxidants, anti-inflammatories, anti-tumor agents, anti-asthmatics, antivirals (including anti-HIV), anti-depressant and anti-coagulants. indole skeletons are widely found in nature and regarded as compound of immense importance. The indole fused coumarins are found to be efficient against tumor angiogenesis which is a key step for spreading out of cancer cells. Therefore, the synthesis of this class of compounds is relevant to drug discovery. On the other hand, construction of C-C bonds, an indispensable part of all organic compounds, *via* cross-dehydrogenative coupling (CDC) reactions is a green and sustainable alternative for synthetic organic chemist because CDC reactions are free from the requirement of any prefunctionalized starting materials. In this context, considering both, the importance and prospective of indole fused coumarins in medicinal chemistry and drug discovery and the need for more sustainable and easily accessible protocol, we, herein, would like to describe the synthesis of indole fused coumarins by palladium-catalyzed CDC reaction (Scheme 2).

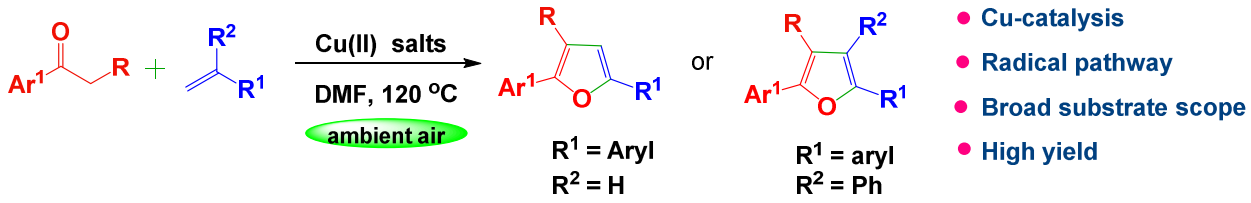
**Conclusion**

In conclusion, we have developed a simple, mild, and efficient palladium-catalyzed cross-dehydrogenative coupling (CDC) reaction of coumarins and anilines, resulting in assembly of substituted indole fused coumarins, from readily available materials without any non-essential pre-functionalization steps. The use of molecular oxygen as an oxidant makes the protocol more sustainable and environmentally benign. Thus, the present method not only serves as a practical, versatile, and atom-economical alternative to existing synthetic methods but also allow facile construction of substituted indole fused coumarin skeletons that have not been easily accessible. Furthermore, these skeletons exhibits important antitumor activity and hence the protocol could lead to access variety of such compounds for further investigations.

### 3. Copper-Catalyzed Regioselective Synthesis of Multisubstituted Furans by Coupling between Ketones and Aromatic Olefins

**Introduction**

A catalytic intermolecular annulation of aryl ketones with a wide range of aromatic olefins has been developed for the regioselective synthesis of multi-substituted furan derivatives. A library of furan derivatives were obtained in good yields from the readily available substrates in the combination of a catalytic amount of Cu-salt under ambient air. This protocol is applicable to both cyclic and acyclic aryl ketones.




**Scheme 3**

Among the five-membered heterocyclic derivatives polysubstituted furan is one of the most important motifs present in a number of pharmaceuticals and biologically active compounds and natural products. On the basis of our experience in copper catalysis, we envisaged that the synthesis of furans might be possible by the annulation of ketones with aromatic olefins via cycloaddition using a catalytic amount of copper salt in the presence of ambient air. Herein we report a regioselective synthesis of 2,3,5-trisubstituted furans from readily available simple aryl ketones and olefins (Scheme 3).

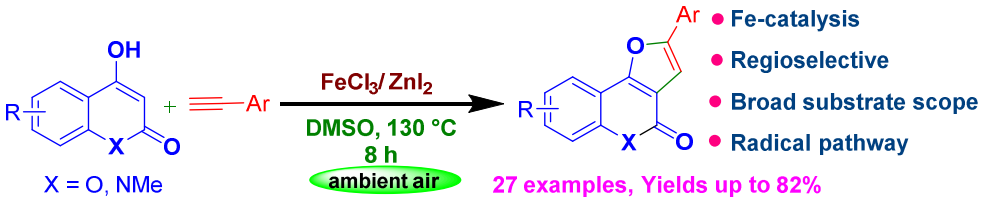
**Conclusion**

In conclusion, we have demonstrated the copper-catalysed annulation *via* free-radical process from aryl ketones and aromatic olefins without using any external oxidant. These reactions provide a novel synthetic route to 2,3,5-tri-, 2,3,4,5-tetrasubstituted furan and 2,2,4,5-tetrasubstituted dihydrofurans from readily available starting materials. Complete regioselectivity, broad substrates scope and wide availablability of starting materials make this protocol synthetically useful to create a library of furan derivatives.

### 4. $FeCl_3/ZnI_2$-Catalyzed Regioselective Synthesis of Angularly Fused Furans

**Introduction**

The $FeCl_3/ZnI_2$-catalyzed synthesis of angularly fused furans by intermolecular coupling between enol and alkyne has been developed under ambient air. The methodology is successfully applicable to 4-hydroxycoumarin, 4-hydroxyquinolinone and $\alpha$-tetralone affording regioselective 2-aryl furans in good yields. The control experiments suggest the possibility of radical reaction mechanism.




**Scheme 4**

Coumarin derivatives have a great importance as a class of heterocyclic compounds and received major attention of organic chemists due to their vital medicinal values, as antivirals (including anti-HIV), anti-tumor agents, antimicrobials, anti-oxidants, anti-asthmatics, anti-coagulants and anti-inflammatories, opto-electronic properties, lipid lowering activity. They are also used in food additives and cosmetic products. Likewise, the furans are also privileged heterocyclic scaffolds of bio-active natural and unnatural compounds. Fusion of these two heterocyclic moieties introduces some unique biological and pharmacological properties in the organic molecules. Herein, we report a simple, atom-economic and concise synthetic approach for the preparation of angularly fused furan derivatives by coupling between arylacetylenes and enols under ambient air (Scheme 4).

**Conclusion**

In conclusion, we have demonstrated a convenient and versatile method for the synthesis of angularly fused furans from arylacetylenes and different enols, including 4-hydroxycoumarins and 4-hydroxyquinolinones with good yields using $FeCl_3/ZnI_2$ catalysts *via* oxidative radical process. The present protocol is also able to produce furan from $\alpha$-tetralone. High regioselectivity, cost-effectiveness, atom-efficiency, broad substrates scope and availability of starting materials are the notable advantages of this method which provides a novel synthetic route to create a library of angularly fused furan derivatives.

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